

REMARKS

I. Status Summary

Claims 1-4, 6-14, 36, 38, and 39 are now pending in the subject U.S. patent application. In an Official Action dated December 18, 2006 (hereinafter the "Official Action"), the United States Patent and Trademark Office (hereinafter "the Patent Office") has withdrawn claim 36, which is believed to be in error. For example, certain rejections under 35 U.S.C. § 103(a) have been applied to claim 36. Consequently, it appears that claim 36 has not been withdrawn, and has been examined along with claims 1-4, 6-14, 38, and 39.

Claims 1, 2, 6-9, 38, and 39 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the claims fail to comply with the written description requirement set forth therein.

Claims 1-3, 7, 8, and 10 have been rejected under 35 U.S.C. § 102(e) upon the contention that the claims are anticipated by U.S. Patent No. 6,670,159 to Savage et al. (hereinafter "the '159 Patent").

Claim 4 has been rejected under 35 U.S.C. § 103(a) upon the contention that the claim is unpatentable over the '159 Patent in view of Zachariou *et al.* (1995) 14 *J Prot Chem* 419-430 (hereinafter "Zachariou"). Claim 6 has also been rejected under this section upon the contention that the claim is unpatentable over the '159 Patent in view of Zhou *et al.* (2000) 11 *J Am Soc Mass Spectrom* 273-282 (hereinafter "Zhou"). Claim 9 has been rejected under this section upon the contention that the claim is unpatentable over the '159 Patent in view of Ehteshami *et al.* (1996) 9 *J Mol Recognition* 733-737 (hereinafter "Ehteshami 1996"). Claims 36, 38, and 39 have also been rejected under this section upon the contention that the claims are unpatentable over the '159 Patent in view of MOLECULAR PROBES™ MP 21879 for the PRO-Q™ Oligohistidine Blot Stain Kit (hereinafter "the PRO-Q™ Technical Literature"). Claims 1, 2, 4, and 7-14 have also been rejected under this section upon the contention that the claims are unpatentable over the 1996 Ph.D. Dissertation of Gholam Ehteshami (hereinafter "the Ehteshami Dissertation") in view of Neville *et al.* (1997) 6 *Prot Sci* 2436-2445 (hereinafter "Neville"). And finally, claims 36, 38, and 39 have also been rejected under this section upon the contention that the claims are unpatentable over

the Ehteshami Dissertation in view of Neville and further in view of the PRO-Q™ Technical Literature.

Withdrawn claims 15-35 have been cancelled without prejudice. Applicant respectfully reserves the right to file one or more divisionals with claims directed to the subject matter of the canceled claims.

Claims 1, 3, 4, 10, and 36 have been amended. Support for the amendments can be found throughout the specification as filed, including particularly on page 17, line 31, to page 18, line 8 (polydentate chelators) and in Figures 7 and 8 (detectable moiety not conjugated to the chelator-metal ion moiety via a coordination site, and tridentate IDA and tetradentate NTA). Additional support can be found in the instant specification at page 22, line 26 through page 23, line 2. Accordingly, applicant respectfully submits that no new matter has been added by the amendments to the claims.

New claims 40-46 have been added. Support for the new claims can be found throughout the specification as filed, including particularly in the claims as originally filed. Additional support can be found on page 17, line 31, to page 18, line 8 (polydentate chelators) and in Figures 7 and 8 (detectable moiety not conjugated to the chelator-metal ion moiety via a coordination site, and tridentate IDA and tetradentate NTA). Accordingly, applicant respectfully submits that no new matter has been added by the inclusion of the new claims.

Reconsideration of the application as amended and based on the remarks set forth herein below is respectfully requested.

II. Comments on the Withdrawal of Claim 36

The Office Action Summary provided with the Official Action states that claim 36 has been withdrawn. Applicant respectfully submits that this would appear to be a typographical error, as claim 36 is directed to subject matter that was part of the election Group in the Response to a Restriction/Election Requirement filed June 29, 2005. Furthermore, claim 36 has been rejected on several bases under 35 U.S.C. § 103(a). Claim 36 was not included in the rejection under 35 U.S.C. § 112, first paragraph, although the two claims that depend from claim 36 (*i.e.*, claims 38 and 39) were rejected under this section.

Accordingly, applicant respectfully submits that it appears that claim 36 has not in fact been withdrawn. In an abundance of caution, applicant will address the rejection under 35 U.S.C. § 112, first paragraph, as if claim 36 had been included in this rejection.

III. Response to the Written Description Rejection

Claims 1, 2, 6-9, 36 (presumptively), 38, and 39 have been rejected under the first paragraph of 35 U.S.C. § 112, upon the contention that the claims fail to comply with the written description requirement. After careful consideration of the rejection and the Patent Office's basis therefor, applicant respectfully traverses the rejection and submit the following remarks.

According to the Patent Office "while the claims reasonably conveys the metal ion, the claims encompass a genus of chelators defined solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property". The Patent Office concedes, however, that:

The specification teaches (page 17, lines 31+) that the term "chelator-metal ion moiety" refers to a polydentate chelator molecule to which a metal ion is coordinated, wherein the polydentate chelator molecule includes, but is not limited to bidentate, tridentate, tetradentate, and pentadentate chelators, and further provides a representative number of polydentate chelator moieties. Thus, while the specification reasonably conveys a representative number of polydentate chelators, there is insufficient written description encompassing the genus of chelators because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics are not set forth in the specification as-filed, and therefore, is not commensurate in scope with the claimed invention.

Official Action at page 3 (emphasis added).

Applicant respectfully submits that in the underlined passage from the Official Action reproduced hereinabove, the Patent Office has conceded that the specification as filed provides a representative number of polydentate chelator moieties, which indicates that as to polydentate chelators, the claims comply with the written description requirement of 35 U.S.C. § 112.

Therefore, to facilitate the instant prosecution, claims 1 and 36 have been

amended to recite *inter alia* that the detection reagent comprises a polydentate chelator. Support for this amendment can be found throughout the specification as filed, including, for example, at page 17, line 31, through page 18 line 8. As such, applicant respectfully submits that no new matter has been added by the amendments to the claims.

Thus, applicant respectfully submits that claims 1 and 36 recite the presently disclosed subject matter in a manner that the Patent Office has acknowledged are exemplified in the instant specification by a representative number of species. As a result, applicant respectfully submits that the instant rejection of claims 1 and 36 has been addressed. Applicant further respectfully submits that the rejection of claims 2, 6-9, 38, and 39, which depend directly or indirectly from claim 1 or claim 36, has also been addressed. Applicant therefore respectfully requests that the instant rejection of claims 1, 2, 6-9, 36, 38, and 39 under 35 U.S.C. § 112, first paragraph, be withdrawn at this time.

#### IV. Response to the Anticipation Rejection

Claims 1-3, 7, 8, and 10 have been rejected under 35 U.S.C. § 102(e) upon the contention that the claims are anticipated by the '159 Patent'. According to the Patent Office, the '159 Patent:

teaches a chelated metal conjugate comprising a chelator having tridentate chelator function towards multivalent metal ions, wherein said chelate is covalently linked via an amide bond to a molecule having a primary amine group (column 2, lines 24-30). With regards to the chelator, the patent teaches that the chelators include, but are not limited to, nitrilotriacetic acid (abstract). With regards to the molecule, the patent teaches that the molecules include, but are not limited to, enzymes, fluorescent labels, biotin or other detectable moieties (column 2, lines 39-41). With regards to the metal, the patent teaches that the metals include, but are not limited to, iron or nickel, wherein iron activated chelate conjugates allows for detection of phosphate-containing molecules (column 4, lines 50-52 and column 10, Example XI). Moreover, the patent teach a method of synthesizing the chelate conjugate comprising reacting nitrilotriacetic acid with a detectable moiety to generate a conjugate and mixing the conjugate with a metal ion-containing solution comprising Fe' (column 4 to column 5, Examples I-II). Thus, while Savage et al. do not explicitly teach that the chelated metal conjugate is soluble in an aqueous medium, the

claims are drawn to the product, per se, and inherently, such a chelated metal conjugate would be soluble in an aqueous medium because the claimed conjugate appears to be the same as the prior art.

Official Action at page 5.

After careful consideration of the rejection and the Patent Office's basis therefor, applicant respectfully traverses the rejection and submit the following remarks.

Applicant respectfully submits that it is axiomatic that to support a rejection under 35 U.S.C. § 102(e), a reference must disclose each and every element of the claims. Applicant respectfully submits that the '159 Patent' does not support a rejection under 35 U.S.C. § 102(e) because the '159 Patent' does not teach a phosphoprotein detection reagent (PPDR) comprising a polydentate chelator and a detectable moiety conjugated to the chelator moiety wherein the detectable moiety is conjugated to the chelator moiety at a site other than a potential metal ion coordination site.

To elaborate, applicant respectfully submits that Formulas I-III of the '159 Patent' clearly show that the detectable moiety (denoted as R, R', or R'') is conjugated to the chelator through one of the coordination sites. Particularly, Formulas I and II of the '159 Patent' show that the NTA moiety is employed as a tridentate chelator, and not a tetradentate chelator. One of the acetate groups, which along with the nitrogen atom are employed in NTA in its tetradentate state to coordinate a metal ion, is employed in the '159 Patent' as a carboxyl functionality to which the detectable moiety is attached via an amide bond. Thus, the '159 Patent' teaches a tridentate NTA.

This is in contrast to the presently disclosed subject matter. In the instant claims, all of the coordination sites of the chelator remain available for coordination of the metal ion. This is shown in Figure 7, which depicts strategies for synthesizing tetradentate NTA and tridentate IDA.

Therefore, applicant respectfully submits that the '159 Patent' does not teach each and every element of independent claims 1 and 10. As such, applicant respectfully submits that the '159 Patent' does not support a rejection of claims 1 and 10 under 35 U.S.C. § 102(e). Claims 2, 3, 7, and 8 all depend from claim 1, and thus are also believed to be distinguished from the '159 Patent'. Accordingly, applicant respectfully requests that the instant rejection of claims 1, 2, 3, 7, 8, and 10 be

withdrawn at this time.

V. Responses to the Obviousness Rejections

Claim 4 has been rejected under 35 U.S.C. § 103(a) upon the contention that the claim is unpatentable over the '159 Patent' in view of Zachariou. Claim 6 has also been rejected under this section upon the contention that the claim is unpatentable over the '159 Patent' in view of Zhou. Claim 9 has been rejected under this section upon the contention that the claim is unpatentable over the '159 Patent' in view of Ehteshami 1996. Claims 36, 38, and 39 have also been rejected under this section upon the contention that the claims are unpatentable over the '159 Patent' in view of the PRO-Q™ Technical Literature. Claims 1, 2, 4, and 7-14 have also been rejected under this section upon the contention that the claims are unpatentable over the Ehteshami Dissertation in view of Neville. And finally, claims 36, 38, and 39 have also been rejected under this section upon the contention that the claims are unpatentable over the Ehteshami Dissertation in view of Neville and further in view of the PRO-Q™ Technical Literature.

After careful consideration of the rejections and the Patent Office's bases therefore, applicant respectfully traverses the rejections and submit the following remarks.

V.A. Response to the Rejection of Claim 4

According to the Patent Office, the '159 Patent' teaches a chelated metal conjugate comprising a chelator having tridenate chelator function towards multivalent metal ions, wherein said chelate is covalently linked via an amide bond to a molecule having a primary amine group (column 2, lines 24-30). The '159 Patent' is also asserted to teach that iminodiacetic acid has been used with iron due to its tight binding characteristics with ferric ions (column 1, lines 35-37). The Patent Office concedes, however, that the '159 Patent' does not explicitly teach that the chelator is iminodiacetic acid.

This deficiency is asserted to be cured by Zachariou, which is asserted to teach that IDA is a tridentate metal chelate (page 428, 2nd column, 8th line from bottom). Specifically, the reference is asserted to teach the purification of proteins using metal

ions bound to IDA, wherein the metal ions include but are not limited to  $\text{Fe}^{3+}$ . The Patent Office thus asserts that it would have been *prima facie* obvious to one of skill in the art at the time the invention was made to combine the teachings of the references because each of metal chelates have been individually taught in the prior art to be effective at protein purification. Moreover, the Patent Office asserts that one would have been motivated to use iminodiacetic acid as the metal chelate because Zachariou teaches that IDA has tridentate functionality. The Patent Office asserts that one of ordinary skill in the art would have a reasonable expectation of success that by substituting IDA which has a high binding affinity for  $\text{Fe}^{3+}$  for NTA as taught by the '159 Patent' in view of Zachariou, one would achieve a metal chelate with high affinity for  $\text{Fe}^{3+}$  which can be used for the detection of phosphoproteins.

This rejection is respectfully traversed. Initially, applicant respectfully submits that Zachariou teaches that IDA chelated with  $\text{Fe}^{3+}$  acts as a reagent for binding to carboxylic acid groups. Given that aspartic acid and glutamic acid contain free carboxylic acid groups, applicant respectfully submits that the disclosure of Zachariou in fact teaches against employing IDA- $\text{Fe}^{3+}$  for detecting phosphoproteins because this reference suggests that the IDA- $\text{Fe}^{3+}$  would be expected to cross react with non-phosphorylated amino acids (*i.e.*, Glu and Asp). It is believed that this would result in a dramatic increase the background (*i.e.*, non-phosphoprotein binding), which would negatively impact the usefulness of the reagents for detection of phosphoproteins.

Applicant further respectfully submits that Zachariou does not cure the deficiencies of the '159 Patent' discussed in more detail hereinabove. Applicant respectfully directs the Patent Office's attention to the discussion hereinabove with respect to the rejection under 35 U.S.C. § 102(e). Summarily, applicant respectfully submits that the '159 Patent' does not disclose or suggest a phosphoprotein detection reagent (PPDR) comprising a polydentate chelator and a detectable moiety conjugated to the polydentate chelator at a site other than a potential metal ion coordination site. As such, even if Zachariou teaches a tridentate IDA, if the NTA of the '159 Patent' were substituted with the IDA of Zachariou, it would no longer be a tridentate IDA because one of the coordination sites of the IDA would be employed as an attachment point for the detectable moiety.

Thus, applicant respectfully submits that if one of ordinary skill in the art were to replace the NTA of the reagent disclosed in the '159 Patent' with IDA as contended by the Patent Office, the IDA would be present in the reagent as a bidentate chelator. Applicant respectfully submits that there is no disclosure in the '159 Patent' that would motivate one of ordinary skill in the art to attach the IDA moiety in any fashion other than via one of the coordination sites as was done for the NTA moiety, and thus the combination of the '159 Patent' and Zachariou would not have motivated one of ordinary skill in the art to produce the subject matter of claim 4.

Accordingly, applicant respectfully submits that the Patent Office has not established a *prima facie* case of obviousness of claim 4 over the combination of the '159 Patent' and Zachariou. Applicant thus requests that the rejection of claim 4 under 35 U.S.C. § 103(a) over the '159 Patent' in view of Zachariou be withdrawn at this time.

V.B. Response to the Rejection of Claim 6

Claim 6 has been rejected under 35 U.S.C. § 103(a) upon the contention that the claim is unpatentable over the '159 Patent' in view of Zhou. The asserted teachings of the '159 Patent' are summarized hereinabove. The Patent Office concedes, however, that the '159 Patent' does not explicitly teach that the metal ion moiety is  $\text{Ga}^{3+}$ . The Patent Office asserts, however, that Zhou teaches the detection of phosphoproteins and peptides using  $\text{Ga}^{3+}$  bound nitrilotriacetic acid and  $\text{Fe}^{3+}$  bound nitrilotriacetic acid (page 275, 1<sup>st</sup> column, 3rd full paragraph). The reference is also asserted to teach that  $\text{Ga}^{3+}$  shows less overall suppression effect and the ability to isolated phosphoproteins with multiple phosphate groups, whereas the selectivity for monophosphorylated peptides is better using  $\text{Fe}^{3+}$  bound nitrilotriacetic acid (page 274, 2nd column, 1<sup>st</sup> full paragraph).

The Patent Office thus contends that it would have been *prima facie* obvious to one of skill in the art at the time the invention was made to combine the teachings of the references so as to optimize the metal ion for a particular phosphoprotein. One would allegedly have been motivated to do so because each of the metal ions bound to nitrilotriacetic acid have been individually taught in the prior art to be effective at detecting phosphorylated proteins. Moreover, the Patent Office asserts that Zhou suggests that the choice of metal ion can be optimized for the highest selectivity towards monophosphorylated proteins versus proteins having multiple phosphate

groups. Thus, the Patent Office asserts that one of ordinary skill in the art would have a reasonable expectation of success that by substituting the metal ion as taught by the '159 Patent for Ga<sup>3+</sup> in view of Zhou, one would achieve a metal chelate which recognizes proteins carrying multiple phosphate groups.

Applicant respectfully submits that the combination of the '159 Patent and Zhou does not support a rejection under 35 U.S.C. § 103(a). Applicant respectfully submits that even if one of ordinary skill in the art were motivated to employ a Ga<sup>3+</sup> in the reagent disclosed in the '159 Patent', that reagent would still at best employ a tridentate NTA since one of the coordination sites is employed for conjugating the detectable moiety. Instant claim 6, however, recites a phosphoprotein detection reagent (PPDR) comprising a polydentate chelator and a detectable moiety conjugated to the polydentate chelator at a site other than a potential metal ion coordination site, which would result in a tetridentate NTA in the instantly claimed reagents.

Accordingly, applicant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claim 6 over the combination of the '159 Patent and Zhou. As such, applicant respectfully requests that the instant rejection be withdrawn at this time.

#### V.C. Response to the Rejection of Claim 9

Claim 9 has been rejected under 35 U.S.C. § 103(a) upon the contention that the claim is unpatentable over the '159 Patent in view of Ehteshami 1996. The asserted teachings of the '159 Patent' are discussed hereinabove. The Patent Office concedes, however, that the '159 Patent' does not explicitly teach that the metal-ion chelate-detectable moiety conjugate further comprises a spacer between the chelator-metal ion and the detectable moiety. This deficiency is asserted to be cured by Ehteshami 1996, which the Patent Office asserts discloses a dual heterofunctional soluble polyethylene glycol conjugate comprising a metal chelator, PEG, and a detectable moiety, wherein the PEG is between the metal chelator and detectable moiety (Abstract). Specifically, the reference is asserted to teach that the presence of the PEG group provides water solubility, but does not affect compounds activity or affinity towards their corresponding conjugate molecules (abstract and page 733, Introduction, 1<sup>st</sup> column, lines 14-15).

The Patent Office thus contends that it would have been *prima facie* obvious to

one of skill in the art at the time the invention was made to combine the teachings of the references so as to incorporate a PEG group between the chelator metal-ion moiety and detectable moiety as taught by the '159 Patent' in view of Ehteshami 1996. The Patent Office asserts that one would have been motivated to do so because Ehteshami 1996 teaches that the presence of the PEG group provides water solubility, but does not affect the compound's activity or affinity towards their corresponding conjugate molecules. As such, the Patent Office contends that one of ordinary skill in the art would have a reasonable expectation of success that by incorporating a PEG group between the chelator metal-ion moiety and detectable moiety as taught by the '159 Patent' in view of Ehteshami 1996, one would achieve a dual heterobifunctional metal-chelate-detectable moiety conjugate which displays greater water solubility and does not affect the compounds activity or affinity towards their corresponding conjugate molecules.

Applicant respectfully submits that the combination of the '159 Patent' and Ehteshami 1996 does not support a rejection under 35 U.S.C. § 103(a). Applicant respectfully directs the Patent Office's attention to the discussion hereinabove with respect to the deficiencies of the '159 Patent'. Particularly, applicant respectfully submits that the '159 Patent' does not teach or suggest a phosphoprotein detection reagent (PPDR) comprising a polydentate chelator and a detectable moiety conjugated to the polydentate chelator at a site other than a potential metal ion coordination site. Applicant further respectfully submits that Ehteshami 1996 does not cure this deficiency.

As such, applicant respectfully submits that even if one of ordinary skill in the art were motivated to introduce a PEG spacer into the reagent disclosed in the '159 Patent', the result would not be the PPDR of claim 9 because the resulting reagent would employ a tridentate NTA, not the tetradebate NTA of the PPDR of claim 9. Therefore, applicant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claim 9 over the combination of the '159 Patent' and Ehteshami 1996, and as a result, applicant respectfully requests that the instant rejection be withdrawn at this time.

V.D. Response to the First Rejection of Claims 36, 38, and 39

Claims 36, 38, and 39 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over the '159 Patent' in view of the PRO-

Q™ Technical Literature. The asserted teachings of the '159 Patent' are discussed hereinabove. The Patent Office concedes, however, that the '159 Patent' does not explicitly teach a kit comprising chelator-metal ion moiety conjugated to a detectable moiety and a secondary reagent for detecting the chelator-metal ion moiety. This deficiency is asserted to be cured by the PRO-Q™ Technical Literature, which is asserted to teach a commercial kit comprising a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, it is contended that the reference teaches (page 1, 1<sup>st</sup> column, Introduction) that the chelator is nitrilotriacetic acid and the metal is Ni<sup>2+</sup>. With regards to the detectable moiety, the PRO-Q™ Technical Literature is asserted to teach that the detectable moiety is biotin (on page 1, 1<sup>st</sup> column, Introduction). The reference is further asserted to teach that the kit further comprises a secondary reagent for detecting the conjugate (1<sup>st</sup> page, 1<sup>st</sup> column, Introduction, lines 11-14), as well as instructions on how to use the kit. Moreover, the PRO-Q™ Technical Literature is asserted to teach that the kit is useful for the detection peptide sequences.

According to the Patent Office, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the chelated metal conjugate as taught by the '159 Patent' into a kit useful for the detection of polypeptides or fragments thereof because a kit would insure standardization of reagents for testing. One of ordinary skill in the art at the time the invention was made allegedly would have been motivated to make a kit useful for the detection of polypeptides or fragments thereof because standard kits enhance the probability of the reproducibility and efficiency of the detection process and further provide for increased marketability, convenience, reliability, and economy.

Applicant respectfully submits that the combination of the '159 Patent' and the PRO-Q™ Technical Literature does not support a rejection under 35 U.S.C. § 103(a) for reasons similar to those discussed immediately hereinabove with respect to the previous rejection. Particularly, applicant respectfully submits that even if one of ordinary skill in the art were motivated to package the reagent of the '159 Patent' into a kit, the kit would not contain a reagent comprising a detectable moiety conjugated to a

polydentate chelator at a site other than a potential metal ion coordination site as presently claimed.

As such, applicant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claim 36 over the combination of the '159 Patent' and the PRO-Q™ Technical Literature. Claims 38 and 39 are dependent from claim 36, and thus are also believed to be distinguished over the cited combination of the '159 Patent' and the PRO-Q™ Technical Literature. As a result, applicant respectfully requests that the instant rejection of claims 36, 38, and 39 be withdrawn at this time

V.E. Response to the Rejection of Claims 1-2, 4 and 7-14

Claims 1, 2, 4, and 7-14 have also been rejected under this section upon the contention that the claims are unpatentable over the Ehteshami Dissertation in view of Neville. According to the Patent Office, the Ehteshami Dissertation discloses in Chapter 5 a heterobifunctional poly (ethylene) glycol derivative having the structure biotin-PEG-IDA and its application in protein purification and characterization using a two phase system. The dissertation is also asserted to teach the effect of IDA in these biochelates for the separation of hemoglobin, a protein with a large number of surface accessible histidines that can interact with the immobilized metal ions and no affinity for biotin (page 126). . With regards to the chelator-metal moiety, the reference is asserted to teach (page 89) that the chelator is iminodiacetic acid (IDA) and the metal is Cu<sup>2+</sup>. The Ehteshami Dissertation is also asserted to teach on pages 83-84 a method of synthesizing the conjugate comprising contacting iminodiacetic acid (IDA) with a molar excess of NHS-biotin under conditions wherein the biotin is transferred to IDA to form the chelator-detectable moiety complex. The Ehteshami Dissertation is further asserted to teach on page 89 that the synthesis step further comprises mixing the IDA-PEG-Biotin conjugate in a metal ion containing solution, wherein the conjugate and metal ion are present in an equimolar concentration. The reference is further asserted to teach that the conjugates are useful for immobilized metal affinity chromatography (IMAC) in the Abstract on page 20.

The Patent Office concedes that the Ehteshami Dissertation does not explicitly teach the metal ion is Fe<sup>3+</sup>. This deficiency is asserted to be cured by Neville, which the Patent Office asserts teaches that Fe<sup>3+</sup>-loaded IDA metal-ion affinity resin binds acidic

and poly-his peptides in addition to phosphopeptides (page 2437, 1<sup>st</sup> column, 3rd paragraph).

As such, the Patent Office asserts that it would have been *prima facie* obvious to one of skill in the art at the time the invention was made to substitute Cu (II) as taught by the Ehteshami Dissertation for Fe<sup>3+</sup> in view of the teachings of Neville. According to the Patent Office, one would have been motivated to do so because each of the metal ions have been individually taught in the prior art to be successful at binding poly-his peptides. Thus, one of ordinary skill in the art is asserted by the Patent Office to have had a reasonable expectation that by substituting Cu(II) as taught by the Ehteshami Dissertation for Fe<sup>3+</sup> as taught by Neville, one would achieve a metal chelate which recognizes poly-His peptides such as hemoglobin.

This rejection is respectfully traversed. Initially, the Patent Office asserts on page 12 of the Official Action that “while the Examiner concedes that Ehteshami Dissertation, as shown in Figure 1.2, that a bioligand and not the chelator metal ion moiety binds to the ligand of interest, the Examiner recognizes that the Ehteshami Dissertation clearly sets forth a charged metal ion IDA-PEG-bioligand, wherein the chelated metal ion binds to the ligand of interest. Therefore, the moiety taught by Ehteshami Dissertation appears to function as the claimed compound of formula 1 in the sense that chelator-metal ion moiety binds to the ligand of interest” (emphasis added). Applicant respectfully submits that the Patent Office is basing this assertion on a selective reading of the Ehteshami Dissertation and is thus not viewing this reference in its entirety as required by M.P.E.P. § 2141.03. Applicant respectfully submits that the reference to the pseudo-affinity chelating effect disclosed on page 126 of the Ehteshami Dissertation is intended to determine a background partitioning of a protein when the copper ion is added, and is not intended to identify a specific binding of the charged reagent.

To elaborate, Chapter 5 of the Ehteshami Dissertation relates to experiments on bioligand-PEG-chelator reagents in a two phase system. In various embodiments, the bioligand is biotin or PAB, which are employed to bind to avidin or trypsin, respectively. On page 131 of the Ehteshami Dissertation, the reference described experiments wherein NH<sub>2</sub>-PEG-IDA and NH<sub>2</sub>-PEG-IDA-Cu(II) were tested for an ability to partition

avidin. The Ehteshami Dissertation discloses “[t]he partition coefficient of avidin in the presence of NH<sub>2</sub>-PEG-IDA-Cu(II) with copper bound was found to be slightly higher than the partition coefficient in the presence of NH<sub>2</sub>-PEG-IDA” (see Ehteshami Dissertation at page 131). It appears that the Patent Office is relying on this disclosure for its assertion that the chelated metal ion binds to the ligand of interest.

However, applicant respectfully submits that this assertion is contrary to the disclosure of the Ehteshami Dissertation when the related discussion is considered in its entirety. For example, immediately following the cited passage, the Ehteshami Dissertation explains the possible basis for the increased partition coefficient of the charged species. Particularly, the Ehteshami Dissertation states that it:

might be due to the fact that when ligand-polymers such as NH<sub>2</sub>-PEG-IDA or NH<sub>2</sub>-PEG-IDA/Cu(II), with low MW (2000), is added to the two-phase systems consisting of high MW PEG's such as PEG8000/salt or PEG8000/Dextran, some of the high MW polymer (e.g. PEG 8000) in the bottom phase will be replaced with the low MW polymer (e.g. ligand-polymer 2000 MW) and will transfer to the top phase. This phenomenon is called "polymer fractionation phenomenon" and the low molecular weight polymer is referred to as sacrificial polymer (Hartounian et al., 1991). According to this phenomenon the lower the molecular weight of the polymer added to the two-phase systems, the higher molecular weight polymer, is replaced in the bottom phase and transfer to the upper phase.

Ehteshami Dissertation at page 131 (emphasis added). Applicant respectfully submits that the clear import of this passage is that the increased partition coefficient is an artifact and does not relate to specific binding of avidin by the charged species as a result as a result of the presence of the metal ion. In fact, applicant respectfully submits that the Ehteshami Dissertation further discloses on page 132 “[a]s it can be seen from Table 5.1-2 the presence of metal ions in bioligands-PEG-IDA-CuR has no significant effect on partitioning of avidin” (emphasis added).

Therefore, applicant respectfully submits that contrary to the Patent Office's assertion, the charged NH<sub>2</sub>-PEG-IDA-Cu(II) species did not bind to the ligand of interest via the chelated metal ion moiety. Furthermore, because the metal ion had no effect on ligand binding, applicant respectfully submits that one of ordinary skill in the art would not have been motivated to employ the Fe<sup>3+</sup> as taught by Neville to purify poly-His peptides such as hemoglobin because the Ehteshami Dissertation teaches against

modifying the metal ion for such purposes as the metal ion was shown to have "no significant effect".

Accordingly, applicant respectfully submits that the proposed combination of the Ehteshami Dissertation and Neville does not support a rejection under 35 U.S.C. § 103(a) of instant claims 1 and 10. Claims 2, 4, 7-9, and 11-14 all depend directly or indirectly from claims 1 and 10, and thus are also believed to be distinguished over the proposed combination of the Ehteshami Dissertation and Neville. As such, applicant respectfully requests that the instant rejection of claims 1, 2, 4, and 7-14 be withdrawn at this time.

V.F. Response to the Second Rejection of Claims 36, 38, and 39

Claims 36, 38, and 39 have also been rejected under this section upon the contention that the claims are unpatentable over the Ehteshami Dissertation in view of Neville, and further in view of the PRO-Q™ Technical Literature. The asserted teachings of the Ehteshami Dissertation in view of Neville are discussed hereinabove. The Patent Office concedes, however, that this combination does not explicitly teach a kit comprising a chelator-metal ion moiety conjugated to a detectable moiety and a secondary reagent for detecting the chelator-metal ion moiety.

This deficiency is asserted to be cured by the PRO-Q™ Technical Literature, which is asserted to disclose a commercial kit comprising a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, the reference is asserted to teach that the chelator is nitrilotriacetic acid and the metal is Ni<sup>2+</sup> (page 1, 1<sup>st</sup> column, Introduction). With regards to the detectable moiety, the PRO-Q™ Technical Literature is asserted to teach that the detectable moiety is biotin (page 1, 1<sup>st</sup> column, Introduction). The reference is further asserted to teach that the kit further comprises a secondary reagent for detecting the conjugate (1st page, 1<sup>st</sup> column, Introduction, lines 11-14), as well as instructions on how to use the kit. Moreover, the PRO-Q™ Technical Literature is asserted to teach that the kit is useful for the detection of peptide sequences.

According to the Patent Office, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to package the chelated

metal conjugate as taught by the Ehteshami Dissertation in view of Neville into a kit useful for the detection of polypeptide or fragment thereof because a kit would insure standardization of reagents for testing. One of ordinary skill in the art at the time the invention was made allegedly would have been motivated to make a kit useful for the detection of polypeptides or fragments thereof because standard kits enhance the probability of the reproducibility and efficiency of the detection process and further provide for increased marketability, convenience, reliability, and economy.

This rejection is respectfully traversed. The Patent Office's attention is directed to the discussion hereinabove with respect to the rejection of claims 1, 2, 4, and 7-14 over the Ehteshami Dissertation in view of Neville. Particularly, applicant respectfully submits that the Ehteshami Dissertation in view of Neville does not teach or suggest the PPDR of claim 1. Therefore, applicant respectfully submits that one of ordinary skill in the art would not have been motivated by the Ehteshami Dissertation in view of Neville and further in view of the PRO-Q™ Technical Literature to create a kit containing the PPDR of claim 1.

Accordingly, applicant respectfully submits that the Patent Office has not presented a *prima facie* case of obviousness of claim 36 over the combination of the Ehteshami Dissertation, Neville, and the PRO-Q™ Technical Literature. Claims 38 and 39 are dependent from claim 36, and thus are also believed to be distinguished over the cited combination of the Ehteshami Dissertation, Neville, and the PRO-Q™ Technical Literature. As such, applicant respectfully requests that the instant rejection of claims 36, 38, and 39 be withdrawn at this time.

#### VI. Discussion of the New Claims

New claims 40-46 have been added. Support for the new claims can be found throughout the specification as filed, including particularly in the claims as originally filed. Additional support can be found on page 17, line 31, to page 18, line 8 (polydentate chelators) and in Figures 7 and 8 (detectable moiety not conjugated to the chelator via a coordination site, and tridentate IDA and tetradentate NTA). Accordingly, applicant respectfully submits that no new matter has been added by the inclusion of the new claims.

New claims 40-46 are believed to be distinguished over the cited references for the reasons set forth hereinabove with respect to the rejections presented against the pending claims. As a result, applicant respectfully submits that claims 40-46 are also in condition for allowance, and respectfully solicits a Notice of Allowance to that effect.

CONCLUSIONS

In accordance with the amendments to the claims and the remarks presented hereinabove, applicant respectfully submits that claims 1-4, 6-14, 36, and 38-46 are in condition for allowance, and respectfully solicits a Notice of Allowance to that effect.

Should there be any minor issues outstanding in this matter, Examiner Fetterolf is respectfully requested to telephone the undersigned attorney. Early passage of the subject application to issue is earnestly solicited.

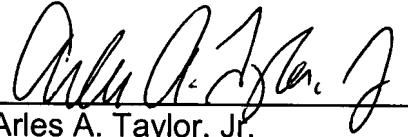
Deposit Account

The Commissioner is hereby authorized to charge any deficiency in payment or credit any overpayment associated with the filing of this correspondence to Deposit Account Number 50-0426.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: 05/18/2007

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